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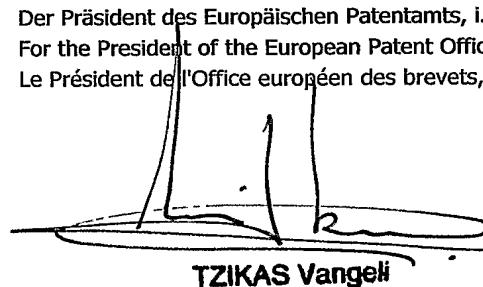
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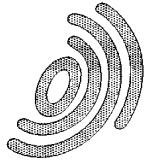
23 -08- 2006

Der Präsident des Europäischen Patentamts, i.A.
For the President of the European Patent Office
Le Président de l'Office européen des brevets, p.o.


TZIKAS Vangelis

Patentanmeldung Nr. PCT/EP2004/002020
Patent application no. PCT/EP2004/002020
Demande de brevet n°





Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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Demande n° :

Anmelder : 1. ACTELION PHARMACEUTICALS LTD - Allschwil, Switzerland
Applicant(s) :
Demandeur(s) :

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ACTELION 59/OR7

Novel Substituted 1,2,3,4-Tetrahydroisoquinoline Derivatives

5

Field of the invention:

The present invention relates to novel substituted 1,2,3,4-tetrahydroisoquinoline derivatives of the general formula (I) and their use as pharmaceuticals. The invention also concerns related aspects including processes for the preparation of the compounds, 10 pharmaceutical compositions containing one or more compounds of the general formula (I), and especially their use as orexin receptor antagonists.

Background of the invention:

Orexins (orexin A or OX-A and orexin B or OX-B) are novel neuropeptides found in 1998 by two research groups, orexin A is a 33 amino acid peptide and orexin B is a 28 amino 15 acid peptide (Sakurai T. *et al.*, Cell, 1998, 92, 573-585). Orexins are produced in discrete neurons of the lateral hypothalamus and bind to the G-protein-coupled receptors (OX₁ and OX₂ receptors). The orexin-1 receptor (OX₁) is selective for OX-A, and the orexin-2 receptor (OX₂) is capable to bind OX-A as well as OX-B. Orexins are found to stimulate food consumption in rats suggesting a physiological role for these peptides as mediators in 20 the central feedback mechanism that regulates feeding behaviour (Sakurai T. *et al.*, Cell, 1998, 92, 573-585). On the other hand, it was also observed that orexins regulate states of sleep and wakefulness opening potentially novel therapeutic approaches to narcolepsy as well as insomnia and other sleep disorders (Chemelli R.M. *et al.*, Cell, 1999, 98, 437-451).

Orexin receptors are found in the mammalian brain and may have numerous implications 25 in pathologies such as depression; anxiety; addictions, obsessive compulsive disorder; affective neurosis; depressive neurosis; anxiety neurosis; dysthymic disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; schizophrenia; manic depression; delirium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Tourette syndrome; eating disorders; sleep disorders; 30 cardiovascular diseases, diabetes; appetite/taste disorders; vomiting/nausea; asthma;

- Parkinson's disease; Cushing's syndrome/disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumour/adenoma; hypothalamic diseases; inflammatory bowel disease; gastric dyskinesia; gastric ulcers; Froehlich's syndrome; hypophysis diseases, hypothalamic hypogonadism; Kallman's syndrome
- 5 (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; sleep disturbances associated with diseases such as neurological disorders,
- 10 neuropathic pain and restless leg syndrome; heart and lung diseases, acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischemic or haemorrhagic stroke; subarachnoid haemorrhage; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated
- 15 sensitivity to pain such as hyperalgesia, causalgia, and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndrome I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain such as irritable bowel syndrome, migraine and angina; urinary bladder incontinence
- 20 e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep apnea; narcolepsy; insomnia; parasomnia; and neurodegenerative disorders including nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration epilepsy; seizure disorders and other diseases related to general orexin system dysfunction.
- 25 The present invention provides substituted 1,2,3,4-tetrahydroisoquinoline derivatives which are non-peptide antagonists of human orexin receptors. These compounds are in particular of potential use in the treatment of e.g. eating disorders or sleep disorders. Up to now, some low molecular weight compounds are known having a potential to antagonise either specifically OX₁ or OX₂, or both receptors at the same time. In some
- 30 patent applications, e.g. SmithKline Beecham reported phenylurea, phenylthiourea and cinnamide derivatives as OX₁ selective antagonists (WO99/09024, WO00/47576 and WO00/47580). More recently, in their patent applications, SmithKline Beecham suggests

2-amino-methylpiperidine derivatives (WO01/96302), 3-aminomethyl-morpholine derivatives (WO02/44172) and N-aroyl cyclic amines (WO02/090355, WO03/002559 and WO03/002561) as orexin receptor antagonists. In WO01/85693, Banyu Pharmaceuticals claimed N-acyltetrahydroisoquinoline derivatives. Other orexin receptor antagonists such 5 as novel benzazepine derivatives are disclosed in WO02/051838.

Actelion Pharmaceuticals Ltd. claimed 1,2,3,4-tetrahydroisoquinoline derivatives and their use as active ingredients in the preparation of pharmaceutical composition (WO01/68609). Furthermore, the use of solution-phase chemistry for the lead 10 optimization of 1,2,3,4-tetrahydroisoquinoline derivatives as potential orexin receptor antagonists has been reported (Chimia, 2003, 57, 1-6).

It is well known that the adequate regulation of plasma concentrations of a drug during the treatment period is one of the crucial aspects in therapy. One very important mechanism for this regulation is the oxidation of a drug substance by cytochrome P450 (CYP) enzymes. The drug oxidation by CYP enzymes should be appropriate with respect to the 15 desired therapeutic indication and a high inhibition of CYP enzymes should be avoided. This is due to the problem of drug-drug interaction, i.e. the increased plasma concentration of a drug by inhibition of a CYP enzyme from another drug.

The predominant drug-metabolising CYP 450s are CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 which represents about 30% of the total CYP enzymes. 20 Many drugs are transformed by CYP3A4 and some drugs have no other metabolism pathway than this specific cytochrome. As a result, a low CYP3A4 inhibition is absolutely crucial for a chemical entity to become a drug candidate.

Description of the invention

It has now been found that the compounds of the present invention have low affinities 25 against CYP3A4. Further, it has also been observed that these compounds were active after oral administration. Compounds of the present invention are therefore useful for the treatment of diseases such as, for example, eating disorders or sleep disorders.

The following paragraphs provide definitions of the various chemical moieties for the compounds according to the invention and are intended to apply uniformly throughout the

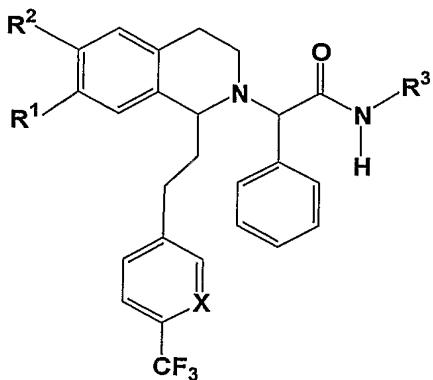
specification and claims unless an otherwise expressly set out definition provides a broader definition.

The term "alkyl", alone or in combination with other groups, means a straight-chain or branched-chain alkyl group with 1 to 6 carbon atoms, preferably a straight or branched-
5 chain alkyl group with 1 to 4 carbon atoms. Examples of straight-chain and branched C_1 - C_6 alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, pentyl, hexyl, the isomeric pentyls, the isomeric hexyls, preferably methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl or *tert*-butyl.

The term "alkoxy", alone or in combination with other groups, means a R-O- group
10 wherein R is an alkyl group as above-defined, such as methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy and *tert*-butoxy, preferably methoxy and ethoxy.

The expression "pharmaceutically acceptable salts" encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid, salicylic acid,
15 succinic acid, trifluoroacetic acid, fumaric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, and the like that are non-toxic to living organisms.

A first aspect of the invention consists of novel substituted 1,2,3,4-tetrahydroisoquinoline
20 derivatives of the following general formula (I):



(I)

wherein

R¹ and R² independently represent hydrogen or C₁-C₄ alkoxy;

R³ represents C₁-C₆-alkyl;

X represents -CH- or a nitrogen atom;

5 and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, meso forms and pharmaceutically acceptable salts, solvent complexes and morphological forms, thereof.

As above-mentioned, the present invention encompasses also solvation complexes of 10 compounds of general Formula (I). The solvation can be effected in the course of the manufacturing process or can take place separately, e.g. as a consequence of hygroscopic properties of an initially anhydrous compound of general Formula (I). The invention further encompasses different morphological forms, e.g. crystalline forms, of compounds of general Formula (I) and their salts and solvation complexes. Particular heteromorphs 15 may exhibit different dissolution properties, stability profiles, and the like, and are all included in the scope of the present invention.

Preferred substituted 1,2,3,4-tetrahydroisoquinoline derivatives are those wherein R¹ and R² both represent a C₁-C₄ alkoxy group, particularly a methoxy group.

In a preferred embodiment according to the invention, X represents -CH-. In another 20 preferred embodiment, X represents a nitrogen atom.

In another preferred embodiment according to the invention, R³ represents a methyl group.

In a particularly preferred embodiment according to the invention, R¹ and R² represent a methoxy group, X represents -CH- and R³ represents C₁-C₆-alkyl.

Examples of preferred compounds are selected from the group consisting of:

25 2-{6,7-Dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-*N*-methyl-2-phenyl-acetamide;

2-{6,7-Dimethoxy-1-[2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-3,4-dihydro-1*H*-iso-quinolin-2-yl}-*N*-methyl-2-phenyl-acetamide.

The compounds pursuant to general formula (I) are useful in the preparation of a medicament for the prevention or treatment of diseases selected from the group consisting of depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis; depressive neurosis; anxiety neurosis; dysthymic disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; schizophrenia; manic depression; delirium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Tourette syndrome; diabetes; appetite/taste disorders; vomiting/nausea; asthma; Parkinson's disease; Cushing's syndrome/disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumour/adenoma; hypothalamic diseases; inflammatory bowel disease; gastric dyskinesia; gastric ulcers; Froehlich's syndrome; hypophysis diseases, hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases, acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischemic or haemorrhagic stroke; subarachnoid haemorrhage; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndrome I and II; arthritic pain; sports injury pain; pain related to infection e.g. by HIV; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain such as irritable bowel syndrome; migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; eating disorders; cardiovascular disorders; neurodegenerative disorders; sleep apnea; narcolepsy; insomnia; parasomnia; and neurodegenerative disorders including nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration epilepsy; seizure disorders and other diseases related to general orexin system dysfunctions.

Compounds of the general formula (I) are particularly suitable for use in the treatment of diseases or disorders selected from the group consisting of eating disorders or sleep disorders.

- Eating disorders may be defined as comprising metabolic dysfunction; dysregulated
- 5 appetite control; compulsive obesities; emeto-bulimia or anorexia nervosa. This pathologically modified food intake may result from disturbed appetite (attraction or aversion for food); altered energy balance (intake vs expenditure); disturbed perception of food quality (high fat or carbohydrates, high palatability); disturbed food availability (unrestricted diet or deprivation) or disrupted water balance.
- 10 Sleep disorders include insomnias, narcolepsy and other disorders of excessive sleepiness, sleep-related dystonias; restless leg syndrome; sleep apneas; jet-lag syndrome; shift-work syndrome, delayed or advanced sleep phase syndrome. Insomnias are defined as comprising sleep disorders associated with aging; intermittent treatment of chronic insomnia; situational transient insomnia (new environment, noise) or short-term insomnia
- 15 due to stress; grief; pain or illness.

A further object of the invention is a pharmaceutical composition containing at least one compound according to general formula (I) and a pharmaceutically acceptable carrier material.

Another object of the present invention is a method for the treatment or prophylaxis of

20 diseases which are related to the orexin receptors such as eating disorders or sleep disorders comprising the administration to a patient of a therapeutically effective amount of a 1,2,3,4-tetrahydroisoquinoline derivative according to general formula (I).

In a preferred embodiment of the invention, this amount is comprised between 1 mg and 1000 mg per day, particularly from 2 mg to 500 mg per day, more particularly from 5 mg to 200 mg per day.

The present invention also concerns a process for the preparation of a pharmaceutical composition comprising a 1,2,3,4-tetrahydroisoquinoline derivative according to general formula (I) by mixing one or more active ingredients according to general formula (I) with a carrier material in a manner known *per se*.

The compounds of general formula (I) and their pharmaceutically acceptable salts can be used as medicament (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered enterally, such as orally (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of suppositories). However, the administration can also be effected parenterally, such as intramuscularly or intravenously (e.g. in the form of injection solutions), or topically, e.g. in the form of ointments, cream or oils.

The compounds of general formula (I) and their pharmaceutically acceptable salts can be processed with pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées, and hard gelatine capsules. Lactose, cornstarch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées, and hard gelatine capsules. Suitable adjuvants for soft gelatine capsules, are for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols, etc.

Suitable adjuvants for the production of solutions and syrups are, for example, water, alcohol, polyols, saccharose, invert sugar, glucose etc. Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils, etc. Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

The above-described components for orally administered or injectable compositions are merely representative examples. Further materials as well as processing techniques and the like are set out in *Remington's Pharmaceutical Sciences*, 20th Edition, 2001, Marck Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

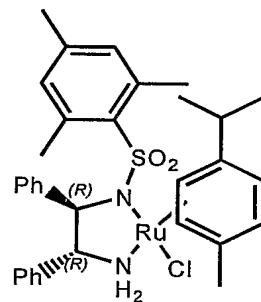
The compounds of this invention can also be administered in sustained release forms by using known sustained release drug delivery systems.

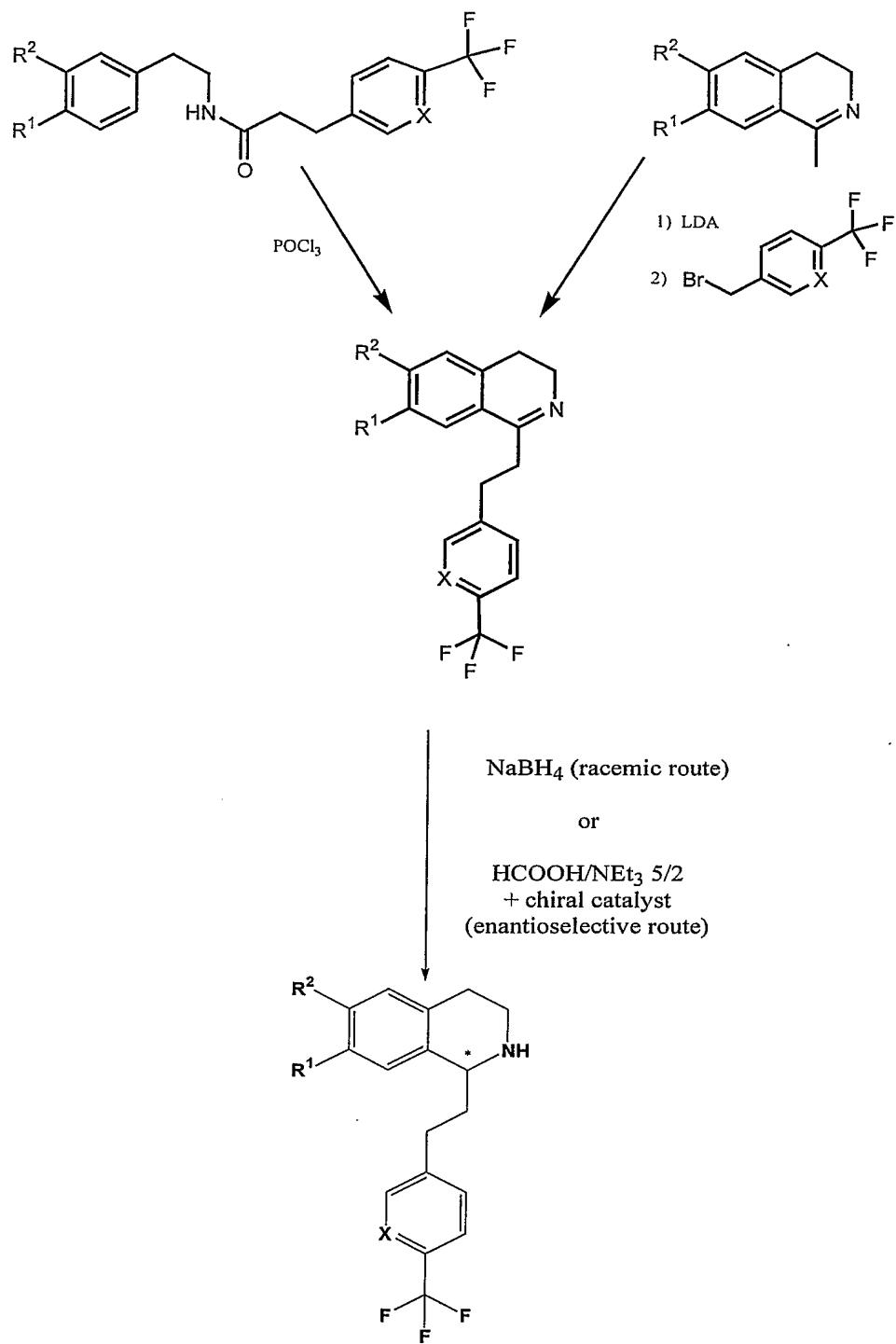
A further object of the invention is a process for the preparation of 1,2,3,4-tetrahydroisoquinoline derivatives according to general formula (I). Compounds according to general formula (I) of the present invention are prepared according to the general sequence of reactions outlined in the schemes below wherein X, R¹, R² and R³ are as defined in

general formula (I). The compounds obtained may also be converted into pharmaceutically acceptable salts thereof in a manner known *per se*.

As described in Scheme 1 below, the key-intermediates in the synthesis of compounds of the general formula (I) are 1-substituted 3,4-dihydroisoquinoline derivatives. These

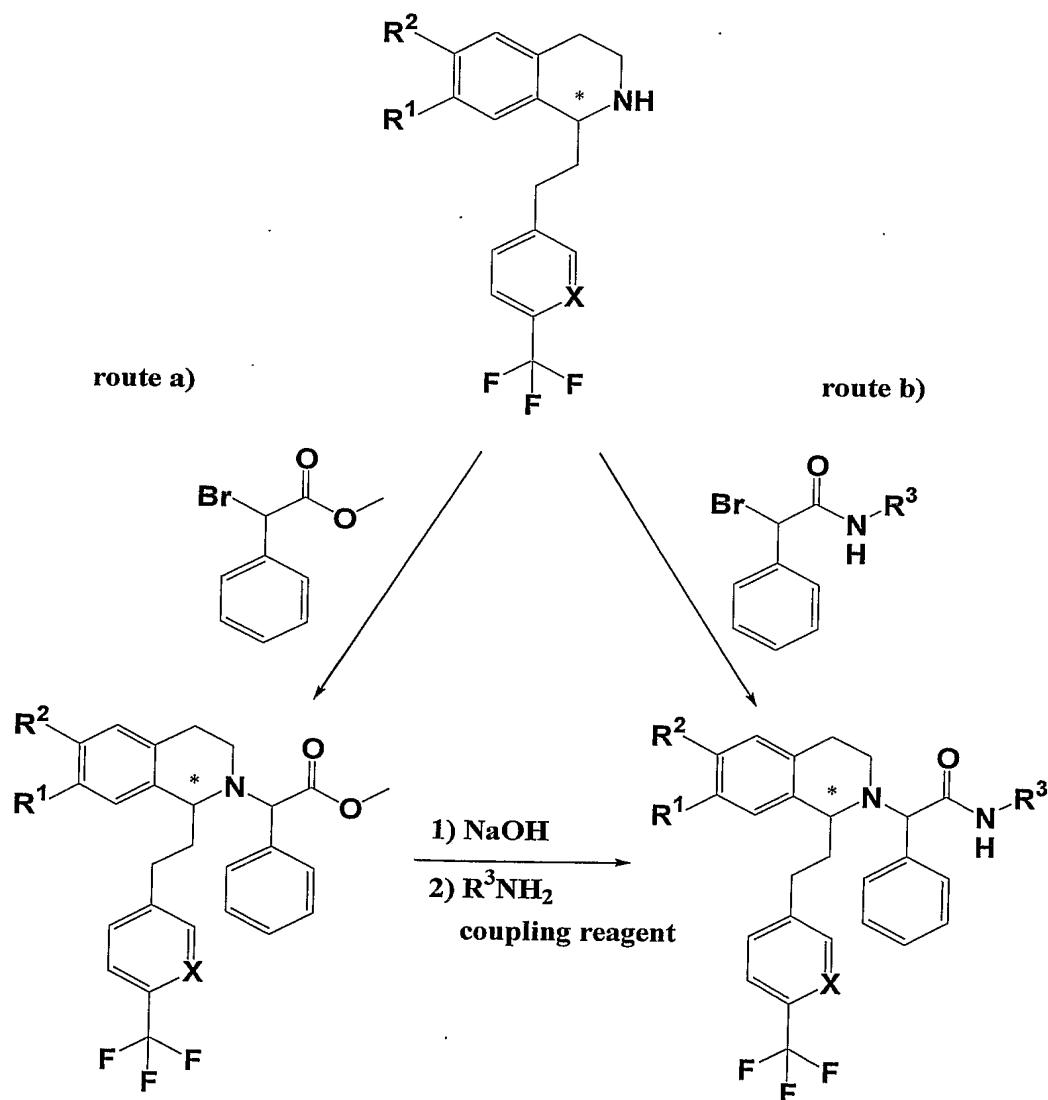
5 compounds are prepared either by cyclisation of *N*-phenethyl-propionamides with POCl_3 or by alkylation of 1-methyl-3,4-dihydroisoquinolines with alkyl bromides. The 3,4-dihydroisoquinolines obtained are reduced to 1,2,3,4-tetrahydroisoquinolines with sodium borohydride to give the products as racemic mixtures. Enantiomerically highly enriched 1,2,3,4-tetrahydroisoquinolines are obtained by a transfer hydrogenation of the respective
10 3,4 dihydroisoquinoline in the presence of a chiral Ru(II)-complex (chiral catalyst), which was originally described by R. Noyori et al. (*J. Am. Chem. Soc.* **1996**, *118*, 4916-4917 and WO 97/20789). The chiral catalyst (Ru(II) complex) used is as follows:



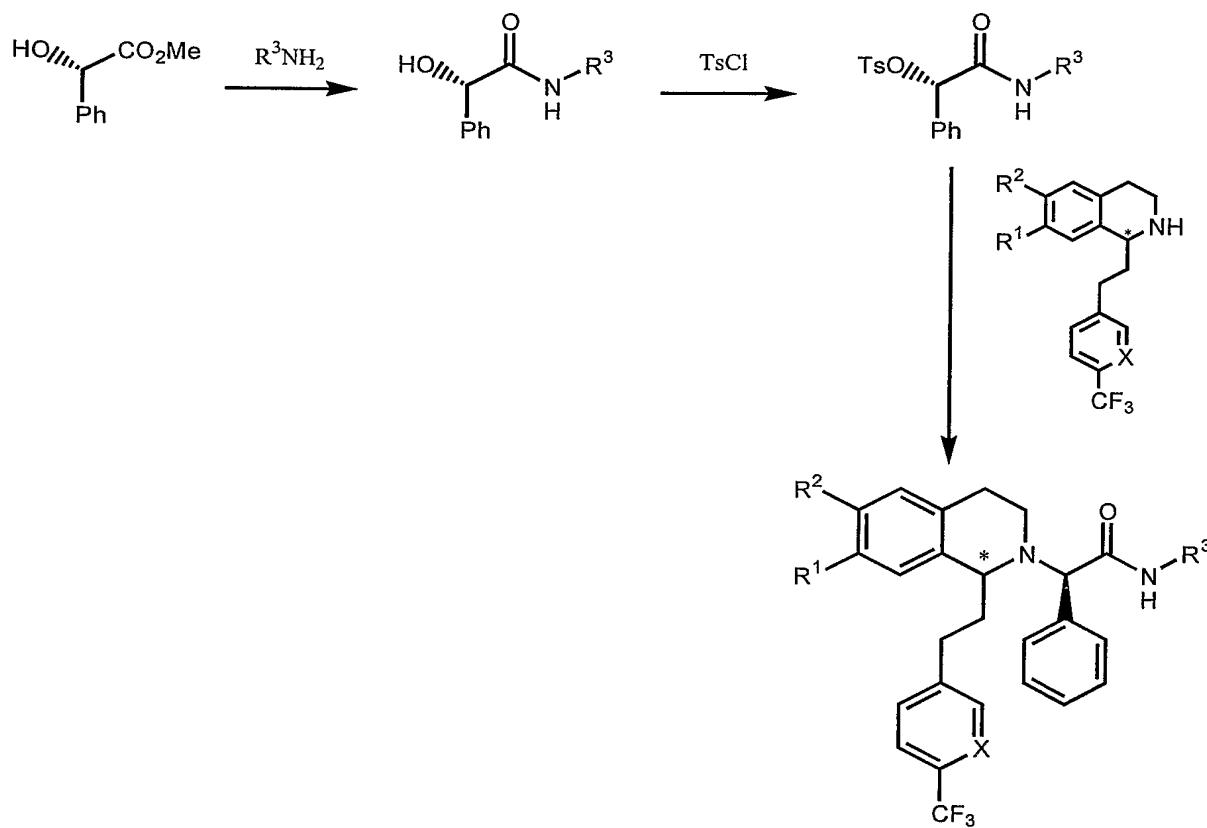


Scheme 1

As illustrated in Scheme 2 and Scheme 3 below, 1,2,3,4-tetrahydroisoquinoline intermediates according to the invention can be converted to compounds of general formula (I) following one of the three different synthetic routes a) b) or c). In route a), the 1,2,3,4-tetrahydroisoquinoline is alkylated with a substituted 2-bromo-acetic acid methyl ester. The obtained ester is hydrolyzed to the corresponding acid and finally converted to the amide by an amide-coupling reaction with the desired amine in the presence of a coupling reagent. In route b), the side-chain is introduced by a direct alkylation of the respective 1,2,3,4-tetrahydroisoquinoline with a 2-bromo-acetamide derivative:



1,2,3,4-tetrahydroisoquinoline derivatives of general formula (I) can also be prepared in a stereoselective manner starting from enantiomerically pure methyl (*S*)-(+)-mandelate following route c) (cf. Scheme 3 hereinafter). By treating the ester with an alcoholic amine solution the corresponding amide is obtained which can be tosylated with 5 *p*-toluenesulphonyl chloride. In a last step the tosylate is coupled with a 1,2,3,4-tetrahydro-isoquinoline derivative to give the respective compound of general formula (I).



The 1,2,3,4-tetrahydroisoquinoline derivatives exemplified in this invention may be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred experimental conditions (i.e., reaction temperatures, time, moles of reagents, solvents, etc.) are given, other 5 experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by one skilled in the art using routine optimisation procedures.

Experimental section:

Abbreviations:

10	aq.	aqueous
	atm	atmosphere
	BSA	Bovine Serum Albumine
	CHO	Chinese Hamster Ovary
	d	Day(s)
15	DCM	Dichloromethane
	DIPEA	Diisopropylethylamine
	DMAP	N,N-dimethyl-4-aminopyridine
	DMF	Dimethylformamide
	DMSO	Dimethylsulfoxide
20	EA	Ethyl acetate
	EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide
	ES	Electron Spray
	FCS	Fetal Calf Serum
	FLIPR	Fluorescent Imaging Plate Reader
25	h	hour
	HBSS	Hank's Balanced Salt Solution
	HEPES	4-(2-Hydroxyethyl)-piperazine-1-ethanesulfonic acid
	HOBt	Hydroxybenzotriazol
	HPLC	High Performance Liquid Chromatography
30	Hex	Hexane
	HV	High Vacuum conditions
	LC	Liquid Chromatography

	LDA	Lithium diisopropylamide
	MeOH	Methanol
	min	minutes
	MS	Mass Spectroscopy
5	p.o.	per os
	prep.	preparative
	PyBOP	Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium-hexafluorophosphate
	R _f	Retention front
10	RT	Room temperature
	rt	retention time
	sat.	saturated
	tlc	thin layer chromatography
	THF	Tetrahydrofuran

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Chemistry

The following examples illustrate the preparation of pharmacologically active compounds of the invention but do not at all limit the scope thereof.

All temperatures are stated in °C.

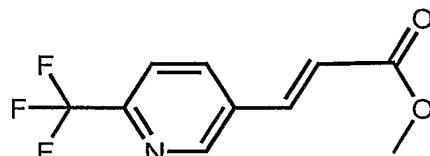
- 20 All analytical and preparative HPLC investigations on non-chiral phases are performed using RP-C18 based columns. Analytical HPLC investigations are performed on two different instruments with cycle-times of ~2.5 min and ~3.5 min respectively. For HPLC separations on chiral phases a Chiralcel OD column from Daicel Chemical Industries is used. Compounds are characterized by ¹H-NMR (300MHz) or ¹³C-NMR (75MHz)
- 25 (Varian Oxford; chemical shifts are given in ppm relative to the solvent used; multiplicities: s = singlet, d = doublet, t = triplet; q = quartet, m = multiplet, b = broad, coupling constants are given in Hz); by LC-MS, rt is given in min; by TLC (TLC-plates from Merck, Silica gel 60 F₂₅₄); or by melting point.

A. Synthesis of propionic acid derivatives:

1. Synthesis of 3-(6-trifluoromethyl-pyridin-3-yl)-propionic acid:

1.1 Synthesis of 3-(6-trifluoromethyl-pyridin-3-yl)-acrylic acid methyl ester:

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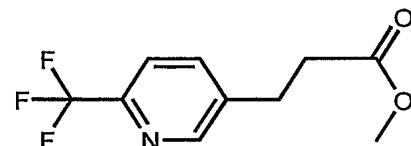


A solution of 6-trifluoromethyl-pyridine-3-carbaldehyde (570 mg) in DCM (1.0 mL) is added to a solution of (triphenyl- λ^5 -phosphanylidene)-acetic acid methyl ester (990 mg) in DCM (2.5 ml). The mixture is stirred under nitrogen at reflux for 20h and concentrated in vacuo. The residue is purified by flash chromatography (EA/heptane 3/7) to give the desired unsaturated ester as a white solid.

¹H-NMR (300MHz, CDCl₃): δ = 3.85 (s, 3H), 6.59 (d, J = 16.2 Hz, 1H), 7.70 (d, J = 16.2 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.98 (dd, J = 8.1 Hz, J = 2.1 Hz, 1H), 8.84 (bs, 1H).

1.2 Synthesis of 3-(6-trifluoromethyl-pyridin-3-yl)-propionic acid methyl ester:

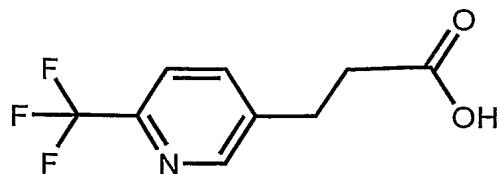
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A solution of 3-(6-trifluoromethyl-pyridin-3-yl)-acrylic acid methyl ester (720 mg) in methanol (5.0 mL) is treated with Pd/C (10%, 240 mg) and stirred under a hydrogen atmosphere (~1 bar) at RT for 20h. The suspension is filtered through Celite and concentrated in vacuo to give the propionic acid ester as a colorless oil.

¹H-NMR (300MHz, CDCl₃): δ = 2.69 (t, J = 7.4 Hz, 2H), 3.05 (t, J = 7.4 Hz, 2H), 3.68 (s, 3H), 7.60 (d, J = 7.8 Hz, 1H), 7.71 (bd, J = 8.1 Hz, 1H), 8.58 (bs, 1H).

1.3. Synthesis of 3-(6-trifluoromethyl-pyridin-3-yl)-propionic acid:



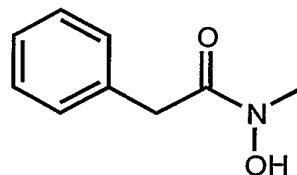
- 5 Lithium hydroxide monohydrate (330 mg) is added in one portion to a solution of 3-(6-trifluoromethyl-pyridin-3-yl)-propionic acid methyl ester (610 mg) in a mixture of THF (15 mL) and water (5 mL). The mixture is stirred for 20h at RT. DCM and aqueous HCl (1.0 M) are added, the layers are separated and the aqueous layer is extracted twice with DCM. The combined organic extracts are dried over MgSO_4 and concentrated in vacuo to give the desired propionic acid as a beige solid.

$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 2.75 (t, J = 7.4 Hz, 2H), 3.06 (t, J = 7.4 Hz, 2H), 7.62 (d, J = 8.1 Hz, 1H), 7.73 (bd, J = 8.1 Hz, 1H), 8.62 (bs, 1H).

B. Synthesis of 2-bromo-acetamide derivatives:

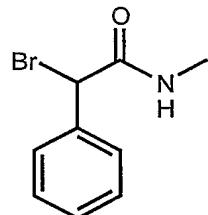
1. Synthesis of 2-bromo-*N*-methyl-2-phenyl-acetamide:

- 15 1.1. Synthesis of *N*-hydroxy-*N*-methyl-2-phenyl-acetamide:



- At 0°C phenyl-acetyl chloride (11.2 mL) is added drop wise to a solution of *N*-methyl-hydroxylamine hydrochloride (7.07 g) and triethylamine (59 mL) in DCM (300 mL). After stirring for 90 min a sat. aqueous NaHCO_3 solution is added, the layers are separated and the aqueous layer is extracted twice with DCM (2x200 mL). The solvents are removed in vacuo and the residue is purified by flash chromatography (EA/heptane 1/1) to give the desired *N*-hydroxy-acetamide as a colorless liquid.
- 25 LC-MS: rt = 0.63 min, 166 (M+1, ES+).

1.2. Synthesis of 2-bromo-*N*-methyl-2-phenyl-acetamide:



- 5 At 0°C triethylamine (5.49 mL) is added to a solution of *N*-hydroxy-*N*-methyl-2-phenyl-acetamide (6.5 g) in DCM (200 mL). The mixture is treated drop wise with a solution of methanesulfonyl chloride (3.21 mL) in DCM (60 mL). After 2 h water (150 mL) is added, the layers are separated and the aqueous layer is extracted twice with EA (2x100 mL). The organic extracts are combined and concentrated in vacuo to give the crude mesylate as a pale yellow oil.
- 10

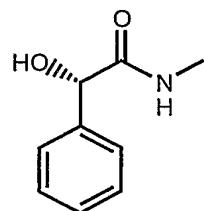
The mesylate is dissolved in acetonitrile (200 mL). Lithium bromide (15.3 g) is added and the reaction mixture is treated with ultrasound for 5 min. After addition of diisopropyl-ethylamine (6.78 mL) the mixture is again treated with ultrasound for 5 min and stirred for additional 60 min at room temperature. Water (150 mL) and ethyl acetate (200 mL) are added, the layers are separated and the aqueous layer is extracted twice with ethyl acetate (2x200 mL). The combined organic extracts are concentrated in vacuo and purified by flash chromatography (ethyl acetate/heptane 2:3) to give the desired bromide as a white solid.

15

LC-MS: rt = 0.75 min, 228 (M+1, ES+).

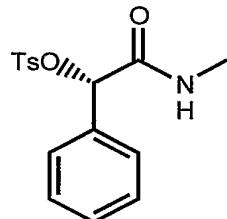
20 **C. Synthesis of toluene-4-sulfonic acid (S)-methylcarbamoyl-phenyl-methyl ester:**

1. Synthesis of (S)-2-hydroxy-*N*-methyl-2-phenyl-acetamide:



Methyl (S)-(+)-mandelate (17 g) is dissolved in a solution of methylamine in methanol (230 mL, 2.0 M) and kept at RT for 1 d. Another portion of methylamine in methanol (10 mL, 2.0 M) is added. A third portion of methylamine in methanol (10 mL, 2.0 M) is added one day later. After additional 24 h the solvents are removed in vacuo to give the desired 5 mandelamide as pale yellow crystals, which are used without further purification.
 LC-MS: $rt = 0.52$ min, 166 (M+1, ES+).

2. Synthesis of toluene-4-sulfonic acid (S)-methylcarbamoyl-phenyl-methyl ester:

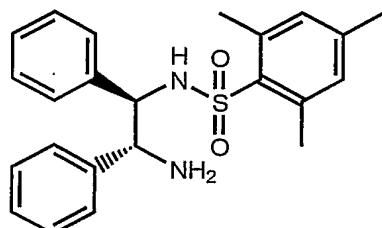


10

At RT DIPEA (2.74 mL) and DMAP (145 mg) are added to a solution of (S)-2-hydroxy-
 N-methyl-2-phenyl-acetamide (2.4 g) in DCM (50 mL). The mixture is treated
 portionwise with p-toluenesulfonyl chloride (2.75 g) and kept for 2 h at RT. The solvent is
 15 removed in vacuo and the residue is dissolved in ethyl acetate. The solution is washed
 twice with sat. $NaHCO_3$ solution and once with brine, the solvents are removed in vacuo
 and the residue is recrystallized from ethyl acetate/tert.-butylmethylether to give the
 tosylate as white crystals.

LC-MS: $rt = 0.93$ min, 320 (M+1, ES+).

20 **D. Synthesis of *N*-((1*R*,2*R*)-2-amino-1,2-diphenyl-ethyl)-2,4,6-trimethyl-benzene-
 sulfonamide (catalyst precursor):**



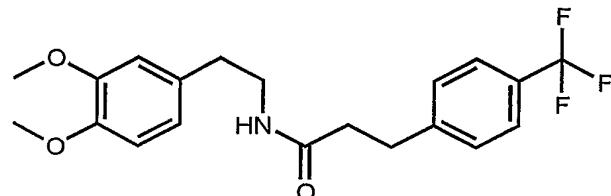
At 0°C a solution of mesitylenesulfonyl chloride (3.09 g) in THF (150 ml) is added drop wise to a suspension of (1R, 2R)-1,2-diphenyl-ethane-1,2-diamine (3.00 g), diisopropylethylamine (3.87 mL) and potassium carbonate (3.12 g) in a mixture of THF (120 mL) and DMF (30 mL). After 3h water (300 mL) and ethyl acetate (300 mL) are 5 added, the layers are separated and the aqueous layer is extracted three times with ethyl acetate (3x300 mL). The solvents are removed in vacuo and the residue is purified by preparative HPLC chromatography. To remove the formic acid the obtained product is extracted with sat. NaHCO₃ solution/ethyl acetate to give the mono-sulfonamide as a white solid.

10 LC-MS: rt = 0.82 min, 395 (M+1, ES+).

E. Synthesis of phenylethylamides (general procedure):

A solution of the respective phenylethylamine (110 mmol) in toluene (350 mL) is treated with the respective propionic acid derivative (110 mmol), refluxed for 90h in the presence of a Dean-Stark trap and cooled slowly to RT. The precipitate is filtered off and dried 15 under vacuum to give the desired amide.

1. Synthesis of *N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-(4-trifluoromethyl-phenyl)-propionamide:

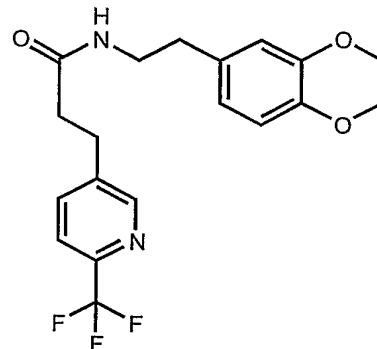


20

This compound is prepared by reaction of 3,4-dimethoxyphenylethylamine and 4-(trifluoromethyl)-hydrocinnamic acid.

LC-MS: rt = 0.97 min, 382 (M+1, ES+).

2. Synthesis of *N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-(6-trifluoromethyl-pyridin-3-yl)-propionamide:



5

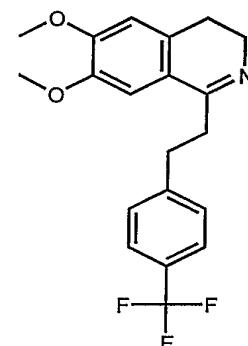
This compound is prepared by reaction of 3,4-dimethoxyphenylethylamine and 3-(6-trifluoromethyl-pyridin-3-yl)-propionic acid.

LC-MS: $rt = 0.88$ min, 383 ($M+1$, ES+).

F. Synthesis of 3,4-dihydroisoquinoline derivatives via amide-cyclisation (general procedure):

10 Phosphorus oxychloride (123 mmol) is added to a suspension of the respective amide (55.3 mmol) in acetonitrile (300 mL). The mixture is refluxed for 90 min and the solvents are removed in vacuo. Methanol (100 mL) is added and evaporated again. The obtained product is recrystallized from dioxane or dioxane/ethanol. After filtration the obtained 15 hydrochloride salt is converted to the free base by addition of saturated aqueous NaHCO_3 solution and extraction with dichloromethane. The solvents are removed in vacuo to give the respective dihydroisoquinoline.

1. Synthesis of 6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydroisoquinoline:



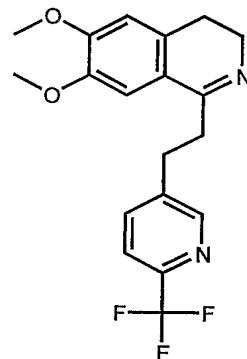
20

This compound is prepared by cyclisation of *N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-(4-trifluoromethyl-phenyl)-propionamide.

LC-MS: rt = 0.81 min, 364 (M+1, ES+).

2. Synthesis of 6,7-dimethoxy-1-[2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-3,4-dihydro-

5 isoquinoline:



This compound is prepared by cyclisation of *N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-(6-

10 trifluoromethyl-pyridin-3-yl)-propionamide.

LC-MS: rt = 0.73 min, 365 (M+1, ES+)

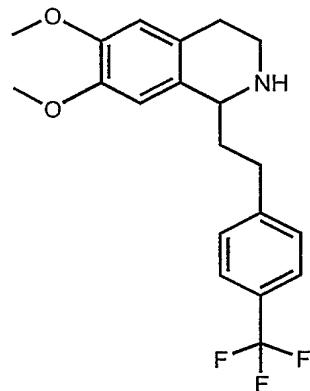
G. Synthesis of 1,2,3,4-tetrahydroisoquinolines:

1. Synthesis of 1,2,3,4-tetrahydroisoquinolines via Bischler-Napieralski-reaction (general procedure):

15 To a suspension of the respective amide (44.8 mmol) in acetonitrile (500 mL) is added phosphorus oxychloride (224 mmol). The mixture is heated to reflux for 2h and the solvent is removed in vacuo. The resulting oil is taken up in either toluene or MeOH (20 mL), evaporated to dryness, dissolved in MeOH (200 mL) and cooled to 0°C. NaBH₄ (135 mmol) is added in small portions and the reaction mixture is stirred for 2h. The

20 solvent is removed in vacuo, EA (400 mL) and water (400 mL) are added, the layers are separated and the aqueous layer is extracted three times with EA (3x200 mL). The combined organic extracts are concentrated in vacuo to give the following 1,2,3,4-tetrahydroisoquinolines as racemic mixtures, which are purified by crystallization of the hydrochloride salt from isopropanol.

1.1. Synthesis of rac-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,2,3,4-tetrahydroisoquinoline:

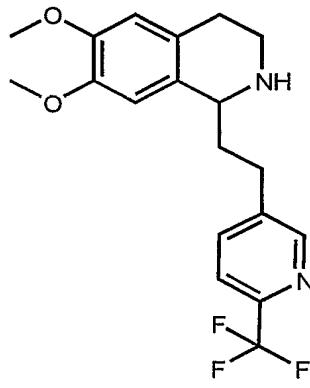


This compound is prepared by reaction of *N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-(4-

5 trifluoromethyl-phenyl)-propionamide.

LC-MS: $rt = 0.85$ min, 366 ($M+1$, ES $+$).

1.2. Synthesis of 6,7-dimethoxy-1-[2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-1,2,3,4-tetrahydroisoquinoline:



10

This compound is prepared by reaction of *N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-(6-trifluoromethyl-pyridin-3-yl)-propionamide.

LC-MS: $rt = 0.73$ min, 367 ($M+1$, ES $+$).

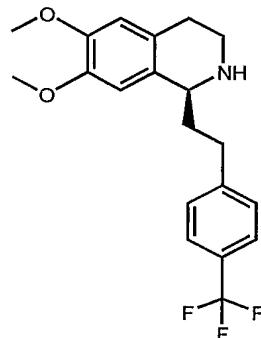
2. Synthesis of 1,2,3,4-tetrahydroisoquinolines via transfer hydrogenation (general procedure):

Dichloro-(*p*-cymene)ruthenium (II) dimer (0.20 mmol) is added to a solution of *N*-((1*R*,2*R*)-2-amino-1,2-diphenyl-ethyl)-2,4,6-trimethylbenzene-sulfonamide (0.40 mmol) and triethylamine (0.80 mmol) in acetonitrile (3.0 mL). The mixture is stirred for 1h at

80°C and added to a solution of the respective dihydroisoquinoline (28.0 mmol) in dichloromethane (30 mL). An azeotropic mixture of formic acid and triethylamine (5:2, 14 mL) is added (gas evolution). After 90 min a sat. aqueous NaHCO_3 solution (200 mL) is added to the dark red solution. The layers are separated, the aqueous layer is extracted twice with DCM (2x200 mL) and the combined organic extracts are concentrated in vacuo. The residue is dissolved in isopropanol (1600 mL) and treated with a solution of HCl in isopropanol (5-6 M, 10 mL). The obtained hydrochloride salt is recrystallized to give the respective 1,2,3,4-tetrahydroisoquinoline with high enantiomeric excess as determined by chiral HPLC. The hydrochloride salt is converted to the free base by extraction with sat. NaHCO_3 solution/dichloromethane. The absolute configuration of the respective product is assigned in analogy to the literature (N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 4916-4917).

2.1 Synthesis of (1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,2,3,4-tetrahydroisoquinoline:

15

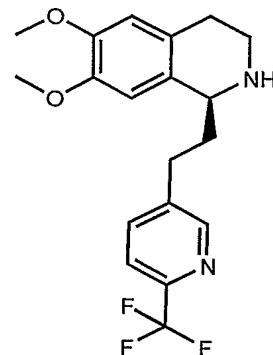


This compound is prepared by transfer hydrogenation of 6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydroisoquinoline.

LC-MS: $rt = 0.80$ min, 366 (M+1, ES+).

20 chiral HPLC: $rt = 12.0$ min (hexane/ethanol 9/1; enantiomer: $rt = 17.1$ min).

2.2 Synthesis of (1S)-6,7-dimethoxy-1-[2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-1,2,3,4-tetrahydroisoquinoline:



- 5 This compound is prepared by transfer hydrogenation of 6,7-dimethoxy-1-[2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-3,4-dihydroisoquinoline.
 LC-MS: $rt = 0.73$ min, 367 ($M+1$, ES+).
 chiral HPLC: $rt = 10.9$ min (hexane/ethanol 4/1; enantiomer: $rt = 24.4$ min).

10 3. Synthesis of 1,2,3,4-tetrahydroisoquinolines via alkylation of 1-methyl-3,4-dihydroisoquinolines (general procedure):

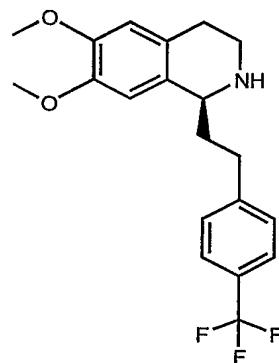
At 0°C a solution of n-BuLi in hexane (1.6M, 0.63 mmol) is added drop wise to a mixture of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (0.50 mmol) and diisopropylamine (0.63 mmol) in THF (1.0 mL). The reaction mixture is stirred at RT for 1h and added at 0°C to a solution of the respective benzyl bromide (0.50 mmol) in THF (1.0 mL). The 15 solution is stirred for 1h, warmed up to RT and diluted with DCM (3.0 mL).

In a second flask dichloro(*p*-cymene)ruthenium (II) dimer (0.15 mmol) is added to a solution of *N*-((1*R*,2*R*)-2-amino-1,2-diphenyl-ethyl)-2,4,6-trimethyl-benzene-sulfonamide (0.30 mmol) and triethylamine (0.60 mmol) in acetonitrile (3.3 mL). The mixture is stirred for 1h at 80°C . A portion of this solution (0.10 mL) is added to the solution of the 20 respective dihydroisoquinoline (described above). An azeotropic mixture of formic acid and triethylamine (5:2, 0.3 mL) is added (gas evolution). After 2d the mixture is concentrated in vacuo and purified by prep. HPLC to give the respective 1,2,3,4-tetrahydroisoquinoline.

The enantiomeric excess is determined by chiral HPLC.

The absolute configuration of the respective product is assigned in analogy to the literature (N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, 118, 4916-4917).

3.1. Synthesis of (1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,2,3,4-tetrahydroisoquinoline:



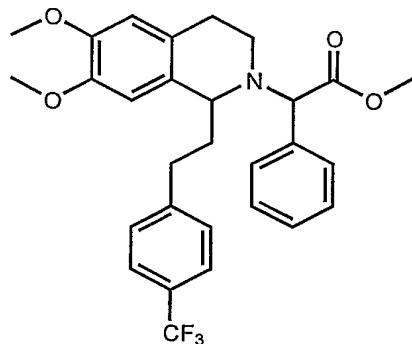
This compound is prepared by alkylation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline with 1-bromomethyl-4-trifluoromethyl-benzene.

10 LC-MS: $rt = 0.80$ min, 366 ($M+1$, ES+).
chiral HPLC: $rt = 12.0$ min (hexane/ethanol 9/1; enantiomer: $rt = 17.1$ min).

H. Synthesis of (3,4-dihydro-1H-isoquinolin-2-yl)-phenyl-acetic acid methyl ester derivatives (general procedure):

DIPEA (43.0 mmol) and α -bromo-phenyl-acetic acid methyl ester (21.5 mmol) are added 15 successively to a solution of the respective 1,2,3,4-tetrahydroisoquinoline (21.5 mmol) in either THF, dioxane or toluene (150 mL). The mixture is refluxed for 20h and allowed to reach RT. Water (250 mL) and EA (200 mL) are added, the layers were separated and the aqueous layer is extracted twice with EA (2x100 mL). The combined organic extracts are concentrated in vacuo and either purified by flash chromatography or used without further 20 purification. The following ester derivatives described hereinafter are obtained.

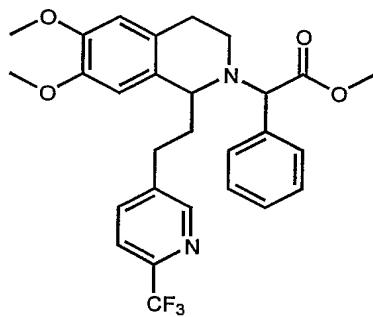
1. Synthesis of {6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-phenyl-acetic acid methyl ester.



- 5 This compound is prepared by reaction of 6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,2,3,4-tetrahydroisoquinoline with α -bromo-phenyl-acetic acid methyl ester.
LC-MS: $rt = 0.93$ min, 514 ($M+1$, ES+).

2. Synthesis of {6,7-dimethoxy-1-[2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-phenyl-acetic acid methyl ester:

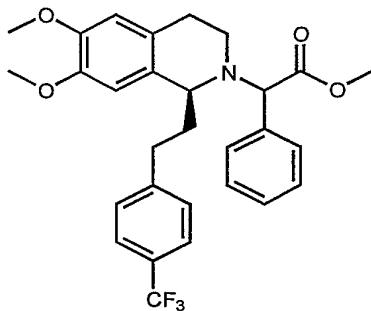
10



This compound is prepared by reaction of 6,7-dimethoxy-1-[2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-1,2,3,4-tetrahydroisoquinoline with α -bromo-phenyl-acetic acid methyl ester.
LC-MS: $rt = 1.68$ min, 515 ($M+1$, ES+).

15

3. Synthesis of {(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-phenyl-acetic acid methyl ester:



5 This compound is prepared by reaction of (1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,2,3,4-tetrahydroisoquinoline with α -bromo-phenyl-acetic acid methyl ester.

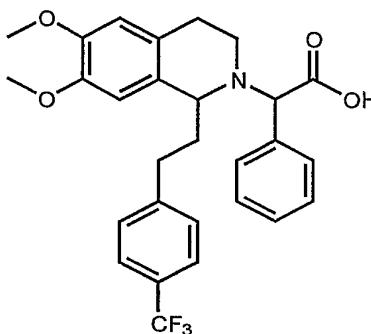
LC-MS: $rt = 0.93$ min, 514 (M+1, ES+).

**I. Synthesis of (3,4-dihydro-1H-isoquinolin-2-yl)-phenyl-acetic acid derivatives
(general procedure):**

10 A solution of sodium hydroxide in water (2.0M, 50 mL) is added to a solution of the respective ester (21.5 mmol) in methanol (400 mL). The mixture is heated to 60°C and stirred for 20h. Most of the methanol is removed in vacuo and the residue is taken up in sodium hydroxide solution (2.0M, 20 mL), water (100 mL) and DCM (100 mL). The 15 layers are separated and the aqueous layer is extracted three times with DCM (3x100 mL). The combined organic extracts are concentrated in vacuo to give the respective carboxylic acid, which is used without further purification:

1. Synthesis of {6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-phenyl-acetic acid:

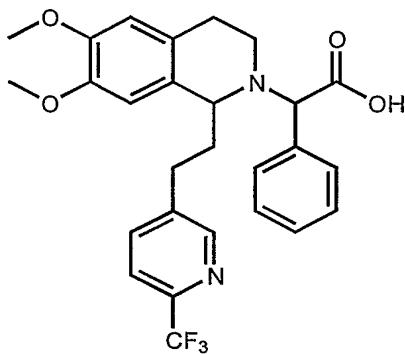
20



This compound is prepared by saponification of {6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-phenyl-acetic acid methyl ester.

LC-MS: rt = 0.88 min, 500 (M+1, ES+).

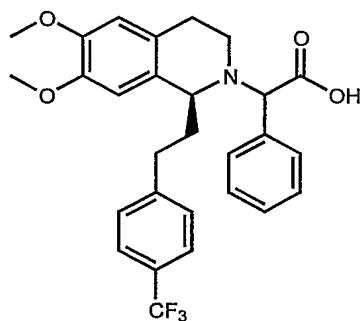
2. Synthesis of {6,7-dimethoxy-1-[2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-3,4-dihydro-
5 1H-isoquinolin-2-yl}-phenyl-acetic acid:



This compound is prepared by saponification of {6,7-dimethoxy-1-[2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-phenyl-acetic acid methyl ester.

10 LC-MS: rt = 1.18 min, 499 (M-1, ES-), 501 (M+1, ES+).

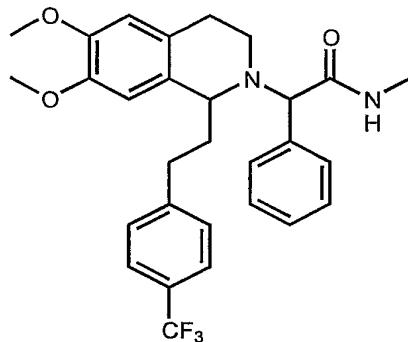
3. Synthesis of {(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-phenyl-acetic acid:



- 15 This compound is prepared by saponification of {(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-phenyl-acetic acid methyl ester.

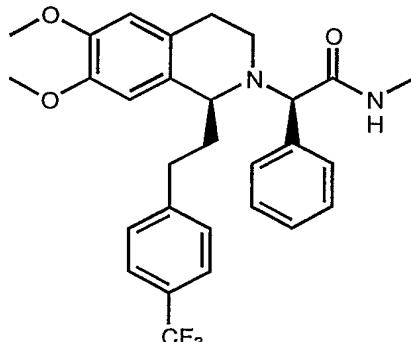
LC-MS: rt = 0.88 min, 500 (M+1, ES+).

Example 1: Synthesis of 2-{6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-methyl-2-phenyl-acetamide



- 5 At 0°C methylamine hydrochloride (15.0 mmol) and NaHCO₃ (20.0 mmol) are added to a solution of {6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-phenyl-acetic acid (10.0 mmol) in DMF (200 mL). After 15 min HOBt (12.0 mmol) and EDC hydrochloride (22.0 mmol) are added. The mixture is stirred for 10 min and kept for additional 14h at 0°C without stirring. Water (100 mL), EA (300 mL)
- 10 and cyclohexane (100 mL) are added, the layers are separated and the aqueous layer is extracted twice with EA/cyclohexane 3:1 (2x150 mL). The combined organic extracts are washed with a sat. aqueous NaHCO₃ solution (100 mL) and brine (100 mL) and dried over Na₂SO₄. The solvents are removed in vacuo and the residue is purified by flash chromatography (gradient: EA/heptane 1/2 to EA/ethanol/heptane 2/1/2) to give the
- 15 desired amides as mixture of all 4 possible stereoisomers.
- LC-MS: rt = 0.89 min, 513 (M+1, ES+).

Example 2: Synthesis of (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-methyl-2-phenyl-acetamide



a) Procedure I (via amide-coupling):

At 0°C methylamine hydrochloride (23.7 mmol) and NaHCO₃ (2.01 g, 23.9 mmol) are added to a solution of {(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-phenyl-acetic acid (21.5 mmol) in DMF (300 mL). After 5 min HOBr (23.8 mmol) and EDC hydrochloride (47.6 mmol) are added. The mixture is stirred for 2h and kept for additional 14h at 0°C without stirring. Water (300 mL) and EA (300 mL) are added, the layers are separated and the aqueous layer is extracted three times with EA (3x150 mL). The combined organic extracts are washed with water (3x100 mL) and brine (100 mL). The solvents are removed in vacuo and the residue is purified by 10 flash chromatography (EA/heptane 3/2) to give the desired amides as separated diastereoisomers.

b) Procedure II (via alkylation with a bromide derivative):

DIPEA (119 mmol) is added to a solution of 2-bromo-N-methyl-2-phenyl-acetamide (59.6 mmol) in THF (150 mL). A solution of (1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,2,3,4-tetrahydroisoquinoline (62.7 mmol) in THF (200 mL) is added and the reaction mixture is stirred at 60°C for 7d. Ethyl acetate (200 mL) and a sat. aqueous solution of NaHCO₃ (200 mL) are added, the layers are separated and the aqueous layer is extracted twice with ethyl acetate (2x100mL). The combined organic extracts are washed with water (3x50 mL), dried over MgSO₄ and concentrated in vacuo. The residue is 20 purified by flash chromatography (ethyl acetate/heptane 3/2) to give the desired amides as separated diastereoisomers.

c) Procedure III (via alkylation with a tosylate derivative):

A solution of (1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,2,3,4-tetrahydroisoquinoline (100 mg), toluene-4-sulfonic acid (S)-methylcarbamoyl-phenyl-methyl ester (100 mg) and DIPEA (0.065 mL) in butanone (5.0 mL) is heated to reflux for 3 d and cooled to RT. Ethyl acetate is added and the mixture is washed with sat. aqueous NaHCO₃ solution and brine. The organic layer is dried over Na₂SO₄ and the solvents are removed in vacuo. THF (2.0 mL) and a solution of HCl in isopropanol (5-6 M, 0.10 mL) are added to the crude product and the solvents are removed in vacuo. The obtained solid 30 is recrystallized from THF (2.0 mL) to give the desired amide as white crystals.

5 Data are given for the free base of the more active diastereoisomer (IC₅₀, FLIPR).

R_f = 0.21 (EA/heptane 2/1);

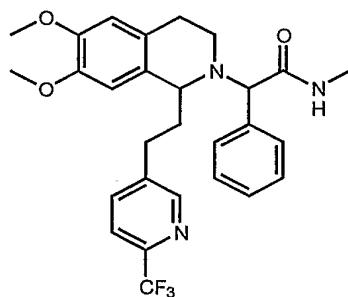
LC-MS: rt = 0.90 min, 513 (M+1, ES+);

Chiral HPLC: rt = 18.9 min (hexane/ethanol 95/5; diastereoisomer: rt = 22.3 min; the two

5 other possible stereoisomers with an opposite configuration in the 1,2,3,4-tetrahydro-isoquinoline ring system are prepared in analogy to the synthesis described above using *N*-(1S,2S)-2-amino-1,2-diphenyl-ethyl)-2,4,6-trimethyl-benzene-sulfonamide (step G.2) for the transfer hydrogenation: these isomers have retention times of: rt = 26.2 min, 33.8 min);

10 ¹H-NMR (300MHz, CDCl₃): δ = 1.74-1.87 (m, 1H), 2.04-2.19 (m, 1H), 2.40-2.52 (m, 1H), 2.59-2.72 (m, 1H), 2.86 (d, J = 4.8 Hz, 3H), 2.86-3.01 (m, 1H), 3.03-3.18 (m, 2H), 3.30-3.41 (m, 2H), 3.69 (s, 3H), 3.84 (s, 3H), 4.25 (s, 1H), 6.03 (s, 1H), 6.57 (s, 1H), 6.87 (q, J = 4.8 Hz, 1H), 7.10-7.16 (m, 2H), 7.19-7.28 (m, 5H), 7.50 (d, J = 8.1 Hz, 2H);
¹³C-NMR (75MHz, CDCl₃): δ = 21.9, 26.1, 33.4, 37.8, 40.7, 55.8, 55.9, 57.0, 70.1, 110.0, 111.4, 124.2 (q, J_{C,F} = 271 Hz), 124.9, 125.1 (q, J_{C,F} = 4 Hz), 128.0 (q, J_{C,F} = 32 Hz), 128.1, 128.4, 128.5, 129.0, 137.0, 146.2, 147.1, 147.6, 172.2.

Example 3: Synthesis of 2-{6,7-dimethoxy-1-[2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-methyl-2-phenyl-acetamide



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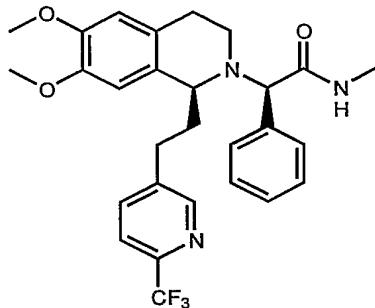
A mixture of {6,7-dimethoxy-1-[2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-phenyl-acetic acid (0.20 mmol), methylamine hydrochloride (0.20 mmol), PyBOP (0.20 mmol) and DIPEA (0.46 mmol) in DMF (1.0 mL) is stirred at RT for 20h. Water and EA are added, the layers are separated and the aqueous layer is extracted with EA. The combined organic extracts are dried over MgSO₄ and concentrated in vacuo. The residue is purified by flash chromatography (EA) to give the desired

product as a viscous oil.

LC-MS: $rt = 1.17$ min, 514 (M+1, ES+).

Example 4: Synthesis of (2R)-2-[(1S)-6,7-dimethoxy-1-[2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl]-N-methyl-2-phenyl-acetamide

5



DIPEA (20.8 mmol) is added to a solution of (1S)-6,7-dimethoxy-1-[2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-1,2,3,4-tetrahydroisoquinoline (10.0 mmol) in THF (40 mL).

10 2-Bromo-N-methyl-2-phenyl-acetamide (10.4 mmol) is added and the mixture is stirred at 60°C for 5d. Water (100 mL) and ethyl acetate (200 mL) are added, the layers are separated and the aqueous layer is extracted twice with ethyl acetate (2x100 mL). The combined organic extracts are concentrated in vacuo and the residue is purified by flash chromatography (ethyl acetate/heptane 3/1) to give the desired amides as separated

15 diastereoisomers.

Data are given for the more active diastereoisomer (IC₅₀, FLIPR).

$R_f = 0.15$ (EA/heptane 3/1);

LC-MS: $rt = 0.81$ min, 514 (M+1, ES+);

¹H-NMR (300MHz, CDCl₃): $\delta = 1.73$ -1.86 (m, 1H), 2.02-2.16 (m, 1H), 2.41-2.52 (m,

20 1H), 2.59-2.71 (m, 1H), 2.87 (d, $J = 5.1$ Hz, 3H), 2.88-3.03 (m, 1H), 3.04-3.17 (m, 2H), 3.26-3.36 (m, 2H), 3.69 (s, 3H), 3.83 (s, 3H), 4.23 (s, 1H), 6.04 (s, 1H), 6.55 (s, 1H), 6.74 (q, $J = 5.1$ Hz, 1H), 7.10-7.16 (m, 2H), 7.19-7.27 (m, 3H), 7.51-7.61 (m, 2H), 8.52 (s, 1H).

Biological assays***In vitro assay***

The orexin receptor antagonistic activity of the compounds of general formula (I) is determined in accordance with the following experimental method.

5 **Experimental method:**• **Intracellular calcium measurements:**

Chinese hamster ovary (CHO) cells expressing the human orexin-1 receptor and the human orexin-2 receptor, respectively, are grown in culture medium (Ham F-12 with L-Glutamine) containing 300 µg/ml G418, 100 U/ml penicillin, 100 µg/ml streptomycin and 10 % inactivated foetal calf serum (FCS). The cells are seeded at 80'000 cells / well into 96-well black clear bottom sterile plates (Costar) which have been precoated with 1% gelatine in Hanks' Balanced Salt Solution (HBSS). All reagents are from Gibco BRL. The seeded plates are incubated overnight at 37°C in 5% CO₂.

Human orexin-A as an agonist is prepared as 1 mM stock solution in methanol: water (1:1), diluted in HBSS containing 0.1 % bovine serum albumin (BSA) and 2 mM HEPES for use in the assay at a final concentration of 10 nM.

Antagonists are prepared as 10 mM stock solution in DMSO, then diluted in 96-well plates, first in DMSO, then in HBSS containing 0.1 % bovine serum albumin (BSA) and 2 mM HEPES.

20 On the day of the assay, 100 µl of loading medium (HBSS containing 1% FCS, 2 mM HEPES, 5 mM probenecid (Sigma) and 3 µM of the fluorescent calcium indicator fluo-3 AM (1 mM stock solution in DMSO with 10% pluronic acid) (Molecular Probes) is added to each well.

25 The 96-well plates are incubated for 60 min at 37° C in 5% CO₂. The loading solution is then aspirated and cells are washed 3 times with 200 µl HBSS containing 2.5 mM probenecid, 0.1% BSA, 2 mM HEPES. 100 µl of that same buffer is left in each well.

Within the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices), antagonists are added to the plate in a volume of 50 µl, incubated for 20 min and finally 100 µl of agonist is added. Fluorescence is measured for each well at 1 second intervals, and the height of each fluorescence peak is compared to the height of the fluorescence peak induced by 10

5 nM orexin-A with buffer in place of antagonist. For each antagonist, IC₅₀ value (the concentration of compound needed to inhibit 50 % of the agonistic response) is determined. Antagonistic activities of compounds are in the nanomolar range.

- Measurements of the inhibitory potency against different CYPs:

The CYP inhibition studies are performed using human liver microsomes (pool of 10

10 individuals), literature-established CYP isoform-selective substrates and quantification by either LC-MS/MS (for CYP3A4 and CYP2C9) or conventional HPLC with fluorimetric detection (for CYP2D6). The specific probes were midazolam 1'-hydroxylation for CYP3A4, dextromethorphan 3-hydroxylation for CYP2D6 and diclofenac 4'-hydroxylation for CYP2C9. Experiments were carried out in duplicate in 96-well plates 15 with substrate concentrations around the respective K_m values (Table 1 shows an overview of the experimental conditions) and 7 inhibitor concentrations up to 50 µM. Controls (sulfaphenazole for CYP2C9, fluoxetine for CYP2D6, and nicardipine for CYP3A4) were run in parallel in each plate.

CYP isoform	substrates and concentration (µM)	microsomal conc. (mg/ml)	incubation time (min)
CYP3A4	midazolam (5)	0.25	5
CYP2C9	diclofenac (5)	0.10	6
CYP2D6	dextromethorphan (8)	0.20	30

As illustrated in Table 2 hereinafter, compounds described in examples 1 to 4 show remarkably low affinities against CYP3A4.

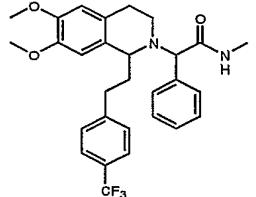
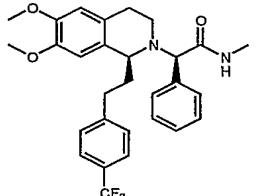
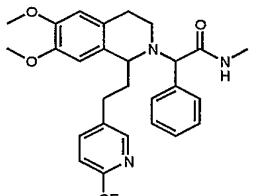
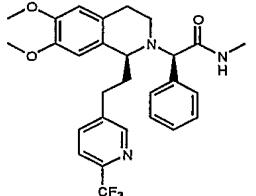
Examples	CYP3A4 IC ₅₀ [μM]
Example 1 	32
Example 2 	46
Example 3 	18
Example 4 	50

Table 2

In vivo assay:**Spontaneous home cage activity and body temperature measured by radiotelemetry in laboratory rats:**

The objective of the present test is to record the circadian behavioral activity of rats after

5 oral administration of a compound according to general formula (I) of the invention.

Decreased home cage activity measured by telemetry in male Wistar rats was considered as an indication for sleep-inducing potential of a restricted number of highly optimized 1,2,3,4-tetrahydroisoquinoline derivatives.

Psychotropic drugs such as antidepressants, antipsychotics, sleep inducers or

10 psychostimulants are well known to reduce or enhance home cage activity and body temperature following oral administration to laboratory animals. Thermoregulation is a complex process that contributes to homeostasis by coordinating metabolism, energy

balance and behaviour. Body temperature changes with circadian behavioural activity and increases when locomotion increases. These two parameters were measured by telemetry

15 in conscious freely moving Wistar rats. Anaesthetized animals were implanted, under aseptic conditions, with a body temperature/activity telemetric device into the peritoneal cavity. More than two weeks after the implantation of the telemetry system, data were

collected at 5 minutes intervals during 96 hours. Hourly means were calculated for each

rat. The first 48 h were used as an internal control trace and drug effects were compared

20 to vehicle placebo. This method is validated pharmacologically by measuring amplitude

and time course of both hypoactivity and hypothermia induced by GABA-A receptor

modulators such as zolpidem.

As illustrated in Table 3 hereinafter, administration of orexin receptor antagonists of the present invention such as those described in examples 1 to 4 are orally active.

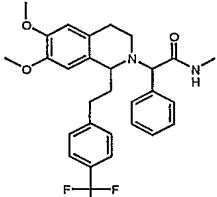
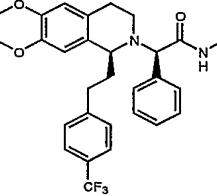
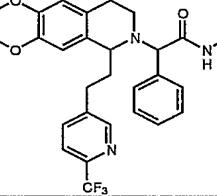
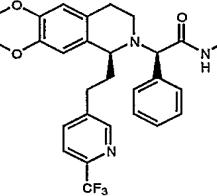
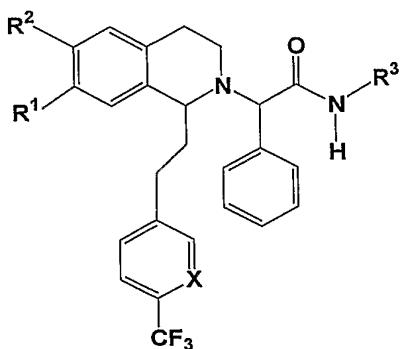
Examples	<i>p.o</i> activity
Example 1 	yes
Example 2 	yes
Example 3 	yes
Example 4 	yes

Table 3

Claims

1. 1,2,3,4-tetrahydroisoquinoline derivatives of the general formula (I)



(I)

wherein:

5 R¹ and R² independently represent hydrogen or C₁-C₄ alkoxy;

R³ represents C₁-C₆-alkyl;

X represents -CH- or a nitrogen atom;

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts, solvent complexes and morphological forms, thereof.

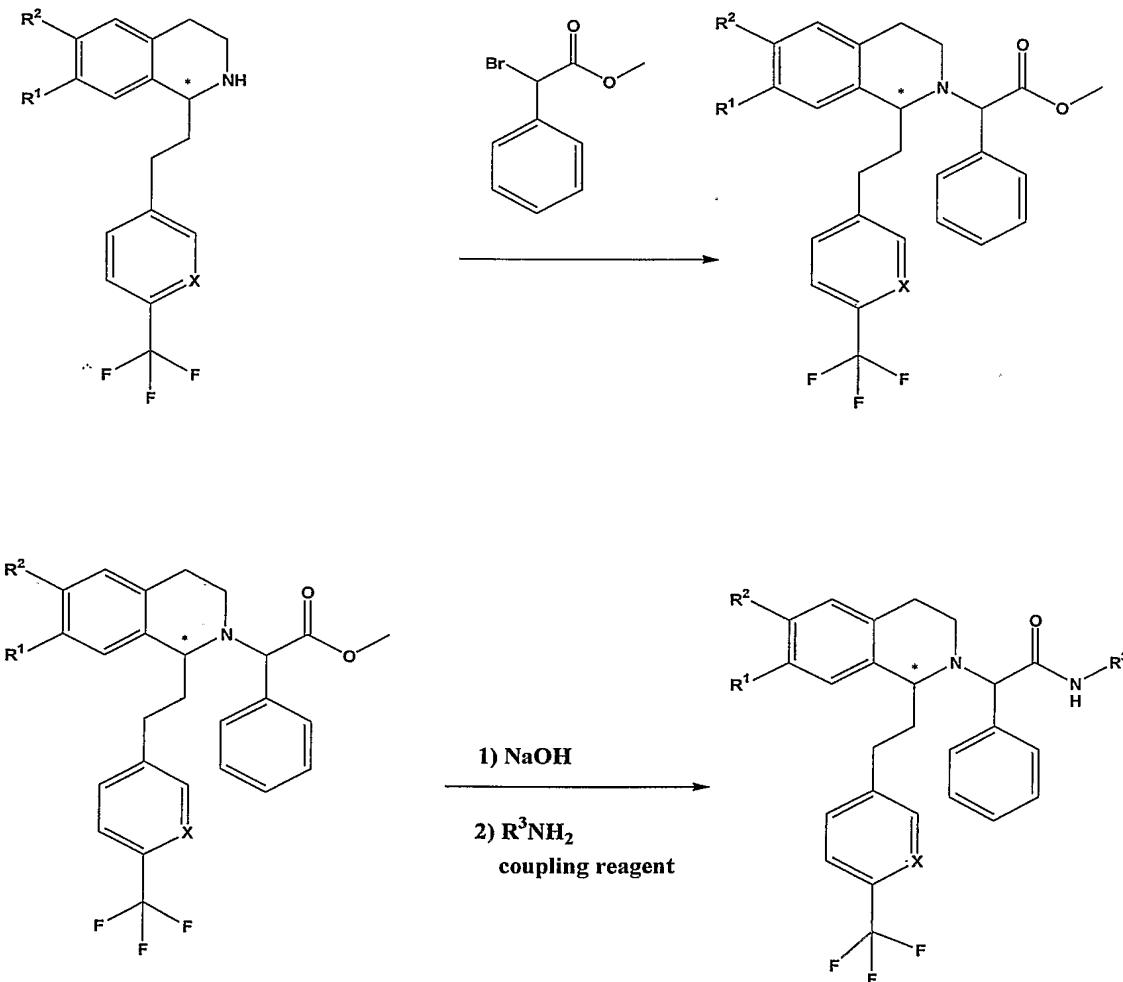
- 10
2. 1,2,3,4-tetrahydroisoquinoline derivatives according to claim 1 wherein R¹ and R² both represent a C₁-C₄ alkoxy group.
3. 1,2,3,4-tetrahydroisoquinoline derivatives according to claim 2 wherein R¹ and R² both represent a methoxy group.
- 15
4. 1,2,3,4-tetrahydroisoquinoline derivatives according to any of claims 1 to 3 wherein X represents a nitrogen atom.
5. 1,2,3,4-tetrahydroisoquinoline derivatives according to any of claims 1 to 3 wherein X represents -CH-.
- 20
6. 1,2,3,4-tetrahydroisoquinoline derivatives according to any of claims 1 to 5 wherein R³ represents a methyl group.

7. 1,2,3,4-tetrahydroisoquinoline derivatives according to any of claims 1, 2, 3 or 5 wherein R¹ and R² represent a methoxy group, X represents -CH- and R³ represents C₁-C₆-alkyl.
8. A 1,2,3,4-tetrahydroisoquinoline derivative according to any of the claims 1 to 3 selected from the group consisting of:
 - 2-{6,7-Dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1*H*-iso-quinolin-2-yl}-*N*-methyl-2-phenyl-acetamide;
 - 2-{6,7-Dimethoxy-1-[2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-3,4-dihydro-1*H*-iso-quinolin-2-yl}-*N*-methyl-2-phenyl-acetamide.
9. A 1,2,3,4-tetrahydroisoquinoline derivative according to any of the preceding claims for use as medicament.
10. A pharmaceutical composition containing at least one compound according to any of claims 1 to 8 and a pharmaceutically acceptable carrier material.
11. Use of a 1,2,3,4-tetrahydroisoquinoline derivative according to any of claims 1 to 8 in the preparation of a medicament for the prevention or treatment of diseases selected from the group consisting of depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis; depressive neurosis; anxiety neurosis; dysthymic disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; schizophrenia; manic depression; delirium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Tourette syndrome; diabetes; appetite/taste disorders; vomiting/nausea; asthma; Parkinson's disease; Cushing's syndrome/disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumour/adenoma; hypothalamic diseases; inflammatory bowel disease; gastric dyskinesia; gastric ulcers; Froehlich's syndrome; hypophysis diseases, hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases, acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischemic or haemorrhagic stroke; subarachnoid haemorrhage; ulcers; allergies; benign

- prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndrome I and II; arthritic pain; sports injury pain; 5 pain related to infection e.g. by HIV; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain such as irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; 10 eating disorders; cardiovascular disorders; neurodegenerative disorders; sleep apnea; narcolepsy; insomnia; parasomnia; and neurodegenerative disorders including nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration epilepsy, seizure disorders and other diseases related to general orexin system dysfunctions.
12. Use according to claim 11 wherein said diseases are selected from the group 15 consisting of eating disorders or sleep disorders.
 13. Use according to claim 12 wherein said eating disorders comprise metabolic dysfunction, dysregulated appetite control, compulsive obesities, emeto-bulimia or anorexia nervosa.
 14. Use according to claim 12 wherein said sleep disorders comprise insomnias, 20 narcolepsy and other disorders of excessive sleepiness, sleep-related dystonias, restless leg syndrome, sleep apneas, jet-lag syndrome, shift-work syndrome, delayed or advanced sleep phase syndrome.
 15. A method for the treatment or prophylaxis of diseases which are related to orexin receptor comprising treatment of eating disorders or sleep disorders comprising the 25 administration to a patient of a therapeutically effective amount of a 1,2,3,4-tetrahydroisoquinoline derivative according to any of claims 1 to 8.
 16. A method according to claim 15 wherein said amount is comprised between 1 mg and 1000 mg per day.
 17. A method according to claim 16 wherein said amount is comprised between 2 mg 30 and 500 mg per day.
 18. A method according to claim 17 wherein said amount is comprised between 5 mg and 200 mg per day.
 19. A process for the preparation of a pharmaceutical composition comprising at least

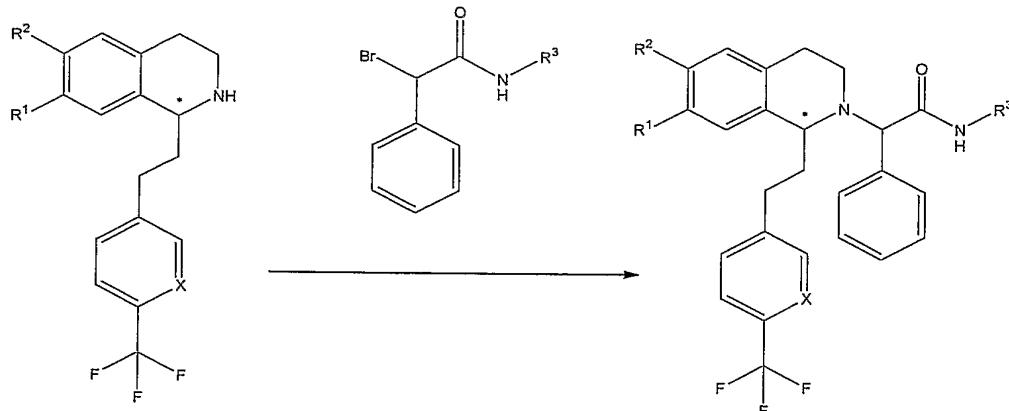
one 1,2,3,4-tetrahydroisoquinoline derivative of the general formula (I) in claim 1, characterized by mixing one or more active ingredients according to general formula (I) with a carrier material in a manner known *per se*.

20. A process for the preparation of a 1,2,3,4-tetrahydroisoquinoline derivative of general formula (I) according to any of claims 1 to 8 comprising the following route a):



wherein X, R¹, R² and R³ are as defined in claim 1.

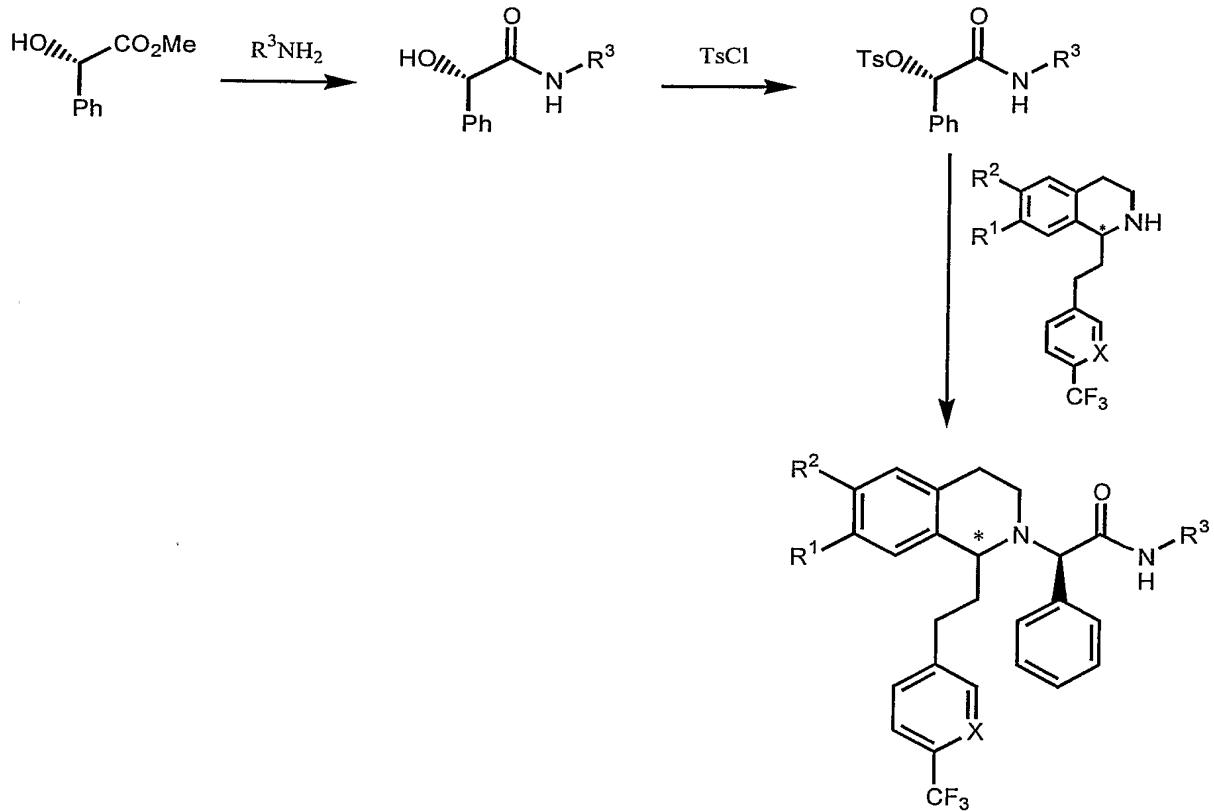
22. A process for the preparation of a 1,2,3,4-tetrahydroisoquinoline derivative of general formula (I) according to any of claims 1 to 8 comprising the following route b):



wherein X , R^1 , R^2 and R^3 are as defined in claim 1.

5

23. A process for the preparation of a 1,2,3,4-tetrahydroisoquinoline derivative of general formula (I) according to any of claims 1 to 8 comprising the following route c):



10

wherein X , R^1 , R^2 and R^3 are as defined in claim 1.

Abstract

The invention relates to novel 1,2,3,4-tetrahydroisoquinoline derivatives and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, 5 pharmaceutical compositions containing one or more of those compounds and methods of treatment comprising administration of said compounds to a mammal.

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